REMARKS

Claims 1, 3-7, and 9-18 are pending. Claims 10-17 are withdrawn from consideration; claims 1, 3-7, 9, and 18 are rejected.

Response to Examiner's Comments on Withdrawn Rejection

As shown on pages 2-3 of the Office Action of November 20, 2009, the rejection of claims 1-9 and 18 under 35 U.S.C. § 103 over Nelles et al. in view of Kobayashi et al. and Georger et al. has not been maintained in view of the new grounds of rejection. Still, the Examiner has made several comments regarding the merits of Applicants' arguments and the Rule 132 Declaration filed September 2, 2009. Namely, the Examiner states that the Declaration is insufficient to overcome the rejections for two reasons.

First, the Examiner states that it is mere speculation that the method of Nelles would damage the cells. Further, the Examiner states that the claimed invention does not require any feature of cells not being damaged during the transferring step.

Second, the Examiner states that it is not correct that the cells embedded on a matrix cannot be dislodged without enzymatic treatment. Nelles is cited as teaching at least two ways of dissociating cells from the matrix: enzymatic degradation (enzyme treatment) and lowering the temperature below the gel-transition temperature (thermogelling polymers) ([0037]). The Examiner maintains that a person of ordinary skill in the art would utilize thermogels which do not require enzymatic degradation to dissociate cells from the matrix.

Applicants respond to the Examiner's comments as follows.

First, one of ordinary skill in the art would understand that a pattern of cells treated by the enzymatic degradation of Nelles (for example, recited in Claim 28) is damaged more severely than a pattern of cells not treated by the enzymatic degradation.

In Nelles, enzymes are used for the degradation of a matrix, which are preferably made of proteins like fibrin and collagen ([0028]). These enzymes inevitably degrade membrane proteins present on the surface of the cells besides the matrix. As such, when a matrix is degraded by an enzyme, a pattern of cells on the matrix is exposed to degradation of membrane proteins of the cells. Membrane proteins usually provide important functions of the cells. As such, the degradation of membrane proteins leads to a loss of function of the cells, which means that the cells are damaged. It is self-evident (and evident to a skilled artisan) that a pattern treated by enzymatic degradation would be damaged more severely than a pattern of cells not treated by enzymatic degradation.

Second, even in consideration of the alleged alternative way suggested by the Examiner, Nelles still fails to suggest the advantageous effect of the present invention.

Nelles discloses in Claim 28 and [0037] that releasing a pattern from the matrix is achieved by lowering the temperature below the gel-transition temperature. Nelles, however, offers no specific explanation of how to implement such releasing. Only a matrix gel which forms its gelled state above its gel-transition temperature can be used for this purpose. Since agarose gel is cured (*i.e.*, gelled) by allowing it to cool, it cannot be used for the purpose (see [0048]). Nelles also discloses in [0049] that collagen-gel can be formed by self-assembly of collagen molecules upon warming cold neutral solutions of collagen. However, to the best of Applicants' knowledge, it is not known that a collagen-gel is able to change back to its solution state simply by lowering the temperature below the gel-transition temperature. In addition, it is not known that a fibrin-gel is able to change back to its solution state simply by lowering the temperature below the gel-transition temperature.

Further, there are technical problems associated with simply lowering the temperature to dissolve a collagen-gel back into a solution because such a course would take an unacceptably long time. Being placed in a temperature lower than a usual cell growth temperature (37 °C) for the time required to achieve the above would damage a cell, as is well known in this technical field. As such, even the suggested alternative way for releasing a pattern of cells out of a matrix by lowering the temperature would still damage the pattern of cells.

In the transferring step recited in the method of claim 1 of the present application, by contrast, it is not necessary to lower the temperature. Thus, the method of the present invention gives the pattern of cells much less damage than the method of Nelles.

Finally, the Examiner appears to mischaracterize the disclosure of Nelles. In particular, Nelles does not disclose a "thermogelling polymer" or "themogel" as asserted by the Examiner. Applicants submit that the Examiner has stretched the meaning of the disclosures of the reference beyond the authors' intention.

Applicants recognize that the rejection of claims 1-9 and 18 under 35 U.S.C. § 103 over Nelles et al. in view of Kobayashi et al. and Georger et al. has been withdrawn. The comments above are provided so as to clarify the record.

Response to Rejection under 35 U.S.C. § 103

Claims 1, 3-7, 9, and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Georger et al. (US 5,324,591) in view of Kobayashi et al. (US 6,294,313) and Singhvi et al. (US 5,776,748).

Georger is cited as teaching a method of culturing cells such as endothelial cells on patterned surfaces (ultra-thin film: UTF) having selective adhesion formed by patterned irradiation (citing Abstract; Fig. 1; cols. 3-4; and col. 13, lines 5-8).

The Examiner characterizes the surface of Georger in the following manner: The UTF is formed on a glass plate coated with EDA (aminosilane), and upon irradiation, the water contact angle of EDA having 28-32° is changed to 92-94° (col. 4, line 65 through col. 5, line 2), providing cell adhesive regions (EDA coated UTF region) and cell non-adhesive regions (pure UTF region). With regard to the regions of Georger, the Examiner takes the EDA layer coated on top of the glass substrate to be a first region (EDA coating; cell adhesive region) formed on a second region (UTF; cell non-adhesive region).

Figure 3 is cited as teaching the pattern formed on the UTF being linear.

The Examiner takes the position that because the UTF can be used as surfaces for body implants (col. 4, lines 19-21), contact of UTF containing cells on a cell adhesive region to the body as an implant would *inherently* transfer cells within the scope of the claims. The Examiner takes the tissue of an implant recipient to be a cell culture substrate in such a case. The Examiner further supports the position by asserting that the force holding the cells on the surface of EDA is weak (mediated by hydrophobic interaction), and upon contact of the cells to the surface having higher binding affinity, the cells would be transferred from the EDA based patterned substrate to that other surface.

Singhvi is cited as teaching a transfer step of cells grown in pattern on a hydrophobic/biophilic surface made of self-assembled monolayer (SAM) such as silicone elastomers including polydimethylsiloxane (PDMS) (col. 18, lines 12-37). The Examiner contends that it would have been obvious to try the transfer process taught by Singhvi for the

cells grown on EDA UTF of Georger to a secondary substrate having higher affinity than the hydrophobic interaction of the cells with EDA UTF.

The Examiner contends that the implantation of cells grown on cell adhesive region (EDA UTF) of Georger is considered to be the same procedure as transferring cells to another substrate having higher affinity to the cells. The Examiner reasons that cell-cell interaction is mediated by various mechanisms including cell adhesion molecules, carbohydrate-carbohydrate interaction, ligand-receptor interaction, *etc.*, known to be much stronger than the hydrophobic interaction of Georger or Singhvi.

As to claims 5 and 6, the Examiner considers the claimed features to have no patentable significance because they allegedly do not recite active steps further defining the method of claim 1.

As to claim 18, the Examiner cited Fig. 3A of Georger as teaching two different types of first regions (cell adhesive region having two different widths; dark regions) and two different types of second regions (cell non-adhesive region having two different widths; white regions).

The rejection should be withdrawn for the following reasons:

(1) Contrary to the Examiner's contention, Georger do not teach or suggest the step of transferring the pattern of cells formed on the UTF to a biological tissue. In addition, the present invention does not intend to use the "cell array substrate" as an implant.

The Examiner asserts at the bottom of page 4 that the claimed transfer step is inherently disclosed because Georger teaches that the ultra-thin films are useful as surfaces for body implants. Applicants dispute the Examiner's assertion in view of the further description of such body implants by Georger. Georger teaches that the device is designed "to influence the subsequent development of tissue on or inside the device" and "might be a surgical implant

material used as an artificial ligament or bone material" (col. 8, lines 3-17). As such, although the Examiner appears to interpret the tissue of an implant recipient as a cell culture substrate, there is no step of transferring in Georger. Instead, the cells arrayed on the UTF surface remain on that surface, which is incorporated into the recipient as an implant material. The cells remaining on the UTF surface are not "transferred" as alleged by the Examiner.

Further, Applicants disagree with the Examiner's opinion that cells adhere to the surface of EDA by means of *weak hydrophobic* interactions. The Examiner contends that cells are adhered to the EDA based patterned substrate by hydrophobic interaction and so would transfer to a surface having higher binding affinity. However, EDA has an amino group, which is a *hydrophilic* moiety and exists in an ionized form under usual cell culture conditions. The cell surfaces have many proteins, which carry a negative net charge. It appears that the charges of EDA and proteins interact with each other to cause the adhesion of the cells to the UTF. In addition, Nelles suggests that EDA has a cell adhesion promoter (column 8, lines 27 to 30). It is not reasonable to assume, as does the Examiner, that the interaction between a cell and EDA with a cell adhesion promoter is a *weak hydrophobic* interaction.

The claims are patentable at least for the reason that Georger does not teach "transferring the adhered cells to a cell culture substrate in the patterned state" as claimed, and the rejection should be withdrawn.

(2) Regarding the combination of Georger and Singhvi, Applicants dispute the reasons for modification cited by the Examiner. Singhvi is directed to a device for adhering cells in a specific and predetermined position (Abstract). The embodiment relied upon by the Examiner requires a specific special orientation of the primary plate, *e.g.*, a 10 x 10 array of 100 islands, for retrieving individual cells. The transfer of cells from the primary plate to the

secondary plate in Singhvi is for the purpose of selecting individual cells positioned on islands of specified coordinates (see, col. 17, ln. 48-49 and 53-57; col. 18, ln. 23-29). That is, the transfer step disclosed in Singhvi is rendered useless where desired cells are not identifiably segregated on the islands of the primary plate. Accordingly, a skilled artisan would not have applied the transfer step of Singhvi to the patterned substrate (see, *e.g.*, Fig. 3A) of Georger.

In addition, Singhvi describes that the secondary plate bears an island with an appropriate biophilic SAM only at a position corresponding spatially to the position of the island (on the primary plate) bearing the desired cell (column 17, lines 49-52). The cell culture substrate used in the present invention has no such complicated structure.

The claims are patentable at least for the reason that a skilled artisan would not have modified Georger and Singhvi as suggested, and the rejection should be withdrawn.

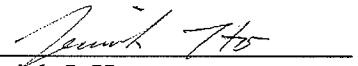
(3) Regarding dependent claims 5 and 6, the Examiner does not adhere to Office procedure by maintaining that the claimed features do not limit the claimed process. The materials on which a process is carried out must be accorded weight in determining the patentability of a process. MPEP 2116, citing *Ex parte Leonard*, 187 USPQ 122 (Bd. App. 1974). Applicants urge the Examiner to attribute weight to the features in accordance with Office procedure.

(4) Regarding dependent claim 18, the Examiner cited Fig. 3A of Georger as teaching two different types of first regions and two different types of second regions, but the Examiner does not allege, and does not show, that Georger teaches "two or more types of cells" as claimed. Applicants traverse the rejection of claim 18 at least for this reason.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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